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**REMARKS**

Reconsideration is respectfully requested. Claims 21-34 were previously pending in the application. Accordingly, claims 21-34 are pending in the application.

**Claim Rejections – 35 U.S.C. § 112**

Claims 21-34 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner has asserted that the specification provides no support for the limitation “chromosomally integrated.”

Applicants respectfully disagree with the Examiner’s rejection. The amendment introduces no new matter. Support for this claim recitation may be found through out the specification. Written description requires only that the specification convey to those skill in the art that applicant at the time of filing the application was in possession of the invention as claimed. This is made explicit by MPEP § 2163.02, which states “the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement.” The amendment adding “chromosomally integrated” was merely to stress what was already claimed. The claim without “chromosomally integrated” read an “animal cell whose genomic DNA comprises at least one copy of a transgene ...” In order for a transgene to be part of the genomic DNA, it must be chromosomally inserted. If the transgene is not chromosomally inserted, then it is floating free as a transiently transfected transgene and therefore is not part of the genomic DNA.

Support for this may also be found within the specification such as in paragraph [0004] which states, “[g]ene expression in transgenic animals is often limited by the position in the genome where the transgene is *integrated* and by the number of copies of the transgene which have been *integrated*.” This sentence clearly refers to transgene that is part of the genome as being “integrated.” Since the genome is made up of chromosomes, integration into the genome and integration into the chromosome is synonymous. However, in order to facilitate prosecution, the

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applicants have amended the claims to remove the word "chromosomally." The specification provides clear support for a transgene that is integrated into the genome.

Thus, the specification provides clear support for the term "integrated." Applicants respectfully request that the examiner withdraw the pending rejection.

**Claim Rejections – 35 U.S.C. § 102(b)**

Claims 21, 23-27, and 30-32 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zhang *et al.*, JBC 270: 8501-8505 (1995) ("Zhang") in view of Ohtani *et al.*, Nucleic Acids Res. 25; 17(4):1589-604, 1989.

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has asserted that Zhang *et al.* teach the inherent incorporation of 50 cells stably transfected with the transgene after five days of culturing. The Examiner bases this assertion upon the teaching of Ohtani *et al.* However, Ohtani *et al.* do not support the assertion that after only *five* days of culturing as taught in Zhang *et al.* was sufficient for stable integration into the genome. Ohtani *et al.* noted that ten days after transfection almost all the cells were killed and only after 14 days were resistant colonies appearing which were still visible only under a microscope (Page 1596, first paragraph). Thus, Ohtani *et al.* only observed stably transfected cells after fourteen days, not after five days. Furthermore, as indicated in the declaration of Dr. Shen provided with this response, even after five days, the vector would not have integrated into the genome.

In addition, Ohtani *et al.* do not support the assertion that Zhang *et al.* taught that 50 cells would have been stably transfected even if the cells were cultured for a sufficient time to for the construct to stably integrate. Ohtani *et al.* and the papers that it cites teach the integration efficiency when conditions are optimized to achieve integration. By way of example, on page 1595, Ohtani *et al.* indicate that "[l]inearized plasmid DNA is, however, known to be more suitable for stable introduction." The plasmid that Zhang *et al.* used was not a linear plasmid, but rather was a circularized plasmid, which would have reduced the frequency of integration.

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The law on inherency is quite clear that the disclosure must *necessarily* disclose the claimed element, not the mere possibility that it may have been present.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (emphasis added).

Thus, the Examiner has not demonstrated that the circularized vector necessarily would have integrated within the five day period and applicants have submitted a declaration stating that it would not have integrated within the five day period.

In order to anticipate a claim under 35 U.S.C. § 102(b), a reference must teach each and every element of a claimed invention. MPEP 2131. As discussed above, the Zhang reference fails to teach each and every element of the claimed invention, specifically the Zhang reference fails to teach an "isolated animal cell whose genomic DNA comprises at least one copy of an *integrated* transgene." As stated above, the construct would not have integrated in the time of the transient transfection assay, so this element has not been met. Thus, this requirement for maintaining a rejection under 35 U.S.C. § 102(b) is not met by the Zhang reference nor by the Ohtani reference, and Applicants respectfully request that this ground for rejection be withdrawn.

#### Claim Rejections – 35 U.S.C. § 103

Claims 21, 23-27, and 30-32 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Zhang et. al., JBC 270: 8501-8505 (1995) ("Zhang") in view of Ohtani *et al.*, Nucleic Acids Res. 25; 17(4):1589-604, 1989.

Applicants respectfully traverse these grounds for rejection. In order to establish a *prima facie* case of obviousness, an examiner must meet three basic criteria: (1) there must be some suggestion or motivation to modify a reference or combine reference teachings, (2) there must be a

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reasonable expectation of success, (3) the references must teach or suggest all claim limitations. MPEP 2142.

Applicants traverse the rejection and its supporting remarks. As discussed above, the cited references do not provide an element of the claims that the vector be integrated into the genome of the animal. Thus, a *prima facie* case has not been established as an element is missing.

Even if a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness may be rebutted by a showing of superior or unexpected results. MPEP 2144.09. As discussed in the applicants' previous responses, the TCTGAGTCA (SEQ ID NO:1) sequence when used in a chromosomally integrated expression construct shows superior and unexpected results by overcoming previous limitations associated with expression of chromosomally integrated constructs (e.g., position-effect variegation, silencing of transgenes, and the inability to increase expression by increasing gene copy number). See, e.g., Sabl et al., Genetics 142:447-458 (1996); Palmer et al., Sharpe et al., EMBO J 11:4565-4572 (1992); and Chen et al., Proc. Natl. Acad. Sci. USA 94:5798-5803 (1997). This is clearly an unexpected result as shown in Table 1 of the specification. Table 1 shows that when the mutant HS-40 transgene is used, a strong positive correlation between copy number of the transgene and hGH expression is observed; in contrast, when the wild type HS-40 transgene is used, increased expression of hGH is not consistently observed with increased copy number. The fact that the wild-type HS-40 element does not provide such position independent expression proves that one of skill in the art would not expect that the presently claimed mutant HS-40 element would provide this result especially given that the wild-type HS-40 element is the closest available enhancer element to the mutant HS-40 presently claimed. Dr. Shen further supports the assertion that this result is unexpected in his Declaration submitted herewith.

As discussed regarding the enablement rejection previously withdrawn by the Examiner, the unexpected result is commensurate with the scope of the pending claims (see pages 7-8 of Applicant's response submitted on December 1, 2003 for a full discussion of the scope of enablement). Dr. Shen in his Declaration submitted on December 1, 2003 provided an abundance

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of evidence supporting the assertion that DNA elements that provide position independent expression act across the animal kingdom and elements from one species will function in widely divergent animal species. Thus, the position independent expression observed with the presently claimed mutant HS-40 element (from a chicken gene that functions in both pig and mouse) will provide the unexpected result commensurate in scope with the present claims.

Finally, the unexpected result is included in the presently pending claims. Therefore, even if the Examiner has established a *prima facie* case of obviousness, this unexpected result would rebut any such claim. Applicants respectfully request that the Examiner withdraw the rejection of claims 21, 23-27, and 30-32 based upon 35 U.S.C. § 103(a) given that the claimed invention provides unexpected results.

The Examiner has asserted that it would not be unexpected that the mutant HS-40 element provides position independent expression. However, the specification clearly indicates that the wild-type HS-40 does not provide position independent expression as is claimed, so one of skill in the art could not expect that the mutant HS-40 as claimed provides position independent expression. It is irrelevant that other elements exist that provide position independent expression. The question is whether the position independent expression provided by the claimed invention is unexpected, which it is. Further, the article Walters *et al.*, PNAS 92:7125-7129, 1995) simply does not support the Examiner's assertion that enhancers generally provide position independent expression. In the introduction on page 7125, Walters *et al.* state that "[i]n stably transfected clones, differences in expression levels are found, but these *are not related to either the number of integrated copies of the construct* or the presence of an enhancer." Thus, Walters clearly indicate that the enhancers that they use do not provide a "level of expression being positively correlated with the copy number of the transgene" as is presently claimed.

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## CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514162000120. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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